

# Cervical Dysplasia Treatment: Key Issues for Developing Countries

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*Many developing countries face serious obstacles that have hindered establishment of successful cervical cancer control programs. Various countries are now seeking to strengthen cytology services and identify simple low-cost screening strategies; but any real gains in reducing cervical cancer incidence and mortality will also require effective treatment of women with preinvasive disease.*

Despite a trend toward conservative outpatient approaches for treating cervical dysplasia in industrialized countries, clinicians in many developing countries still rely primarily on invasive inpatient methods such as cone biopsy and hysterectomy. For women who could be treated with less invasive methods, these procedures tend to pose unnecessary risks and entail high costs that put them beyond the reach of many patients.

Outpatient therapy, employing methods such as cryotherapy and the loop electrosurgical excision procedure (LEEP), combined with proper follow-up, is appropriate for dealing with visible lesions on the ectocervix when invasive cancer and endocervical involvement have been ruled out. Cryotherapy and LEEP hold out particular promise for developing countries because of their effectiveness, lack of side-effects, simplicity, and low cost. Cure rates range from 80% to 95%, depending on the method used and the severity of the lesions. However, each method has advantages and disadvantages that demand consideration. Various ways of reducing the number of follow-up visits, including the two-visit "see and treat" approach, are also available for use in areas where women's access to health services may be limited.

A recent survey by the Program for Appropriate Technology in Health (PATH) affirmed the tendency to rely on cone biopsy and hysterectomy. It also found that in many places all degrees of preinvasive disease were treated, rather than only high-grade or severe conditions; that respondents in Latin America, the Caribbean, and Asia tended to use cryotherapy and LEEP more widely than other low-cost methods; that LEEP was preferred over cryotherapy in Latin America; and that colposcopes and other basic equipment needed to provide treatment were not consistently or widely available in some settings.

Cervical cancer is a leading cause of cancer death among women in developing countries. Worldwide, some 437 000 new cases occur annually, nearly 80% of them in developing countries (1). Within the Americas, over 30 000 women die of

cervical cancer annually (2). Furthermore, as the average ages of populations rise in future decades, the number of cervical cancer cases is likely to increase significantly.

Unlike many other cancers, cervical cancer can be prevented by screening at-risk women and treating preinvasive disease. However, many developing countries face financial, technical, and logistical obstacles that have hindered establishment of successful cervical cancer control programs. During the early 1980s in Brazil, for instance, screening and treatment programs for preinvasive conditions were able to

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cover only 2% of the women at risk (3). In addition, women in many countries tend not to seek medical services until the disease has reached an advanced stage where treatment is expensive and the chances of success are slim. Efforts are now being made in various countries to strengthen cytology services and to identify simple, low-cost alternative screening strategies that may improve early detection of cervical intraepithelial neoplasia (CIN). Any real gains in reducing cervical cancer incidence and mortality, however, will require not just detection but also effective treatment of women with preinvasive disease.

In the industrialized countries, aggressive treatment of all grades of CIN (as defined by cytology) was standard practice until the 1960s. Since then, however, and most notably over the past decade, management of preinvasive cervical conditions has shifted toward conservative outpatient approaches. This has been due to several factors: the introduction of colposcopy; increased knowledge about the natural history of cervical dysplasia; and the availability of effective, low-cost outpatient treatment technologies such as cryotherapy and the loop electrosurgical excision procedure (LEEP) (4, 5).

In contrast, clinicians in many developing countries where diagnosis and treatment are performed still rely primarily on invasive inpatient methods such as cone biopsy and hysterectomy to treat CIN, resulting in the overtreatment of many women. Although appropriate under certain circumstances, these approaches are associated with significant complications and side-effects; and they tend to put women who could be treated with less invasive methods at unnecessary risk of morbidity and mortality. In addition, both conization and hysterectomy are very costly procedures that require significant infrastructure support. They are usually performed at tertiary or university hospitals in urban settings, facilities beyond the reach of many women needing treatment.

As part of an effort to identify rational, cost-effective, and appropriate treatment strategies and technologies for settings with limited resources, the Program for Appropriate Technology in Health (PATH) recently undertook a survey of CIN treatment practices and preferences in selected developing country settings around the world.<sup>3</sup> The survey took place in the period September 1994–March 1995. Survey forms were sent to clinicians and specialists in women's and public health drawn from professional contacts and the literature. No attempt was made to obtain a representative sample of practitioners by region or type of facility. While most of the survey respondents were working in central or provincial facilities, others were working at private missions or other nongovernmental facilities. The survey results therefore provide a picture of prevailing CIN treatment practices primarily in these settings. Based on the survey findings and other available data, this article reviews current treatment strategies and outpatient treatment techniques.

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<sup>3</sup> As part of an overall effort to improve cervical cancer detection and treatment of preinvasive disease, PATH developed a survey questionnaire and mailed it to 238 clinicians and women's health experts through-out the world who may have had some experience in cervical cancer/dysplasia detection and treatment. Some recipients further disseminated the survey to local contacts, thereby increasing its distribution. The purpose of the questionnaire was to assess the availability of current treatment interventions and to help identify low-cost simple treatment alternatives that may be appropriate for low-resource settings and that could be used with simplified screening strategies. Information was also gathered on current screening practices, perceived barriers to screening and follow-up care, personnel requirements, and other logistic concerns. A majority of the respondents (52%) were working in central, provincial, or university hospitals, while 15% were working for nongovernmental organizations, private hospitals, or mission hospitals. Guided interviews were also conducted by PATH staff members in countries where PATH has field offices or associates (Kenya, Sierra Leone, Thailand, and the Philippines).

## CIN MANAGEMENT: CURRENT STATUS

While hysterectomy is still indicated for conditions such as adenocarcinoma *in situ*, selected cases of microinvasion, and all invasive cases, it is now known to be unnecessarily radical for treating CIN. And although cone biopsy (which removes a cone-shaped section of the cervix) is relatively effective in diagnosing and eradicating moderate and severe dysplasia (CIN II and III) and carcinoma *in situ* (CIS), it is associated with significant complications—including immediate and prolonged bleeding, cervical stenosis, and increased incidence of spontaneous miscarriage and obstructed labor in subsequent pregnancies. Cone biopsy may be recommended for women where invasive disease or cervical gland involvement is suspected, as well as for cases where colposcopy is not available and invasive cancer cannot be ruled out by random biopsies or other means (3).

## TREATMENT STRATEGIES: WHICH CIN GRADES SHOULD BE TREATED?

Current understanding of the natural history of CIN, including the etiologic role of the human papillomavirus (HPV), suggests that treatment should be limited to women with moderate and severe dysplasia (CIN II and III) and CIS, since most mild dysplasia will either not progress or will spontaneously revert to normal without therapy (6). According to this strategy, women with mild lesions should be monitored at appropriate intervals, while local destructive or excision therapy should be used only to treat women with moderate or severe lesions. This approach reduces costs and lessens the stress on health care systems that might otherwise be overtaxed by women with mild cervical abnormalities. On the other hand, it requires effective monitoring of women with mild condi-

tions, which may be difficult in some settings.

Other treatment strategies may also be considered—depending on local epidemiology, resource availability, and the local capacity to treat or monitor women. These include limiting treatment to women with severe lesions only (CIN III/CIS) or treating women with low-grade as well as high-grade lesions. Although more controversial, these approaches may be practical and appropriate in some settings as first steps toward expanding CIN treatment services.

## Treating Severe CIN Only

In regions with very scarce resources, programs may opt to refer and treat only women with severe dysplasia in order to lessen the health care burden while still achieving significant health gains. Evidence suggests that CIN II can regress, although at a significantly lower rate than CIN I (7). The appropriateness and cost-effectiveness of this approach, therefore, will depend partly on the proportion of CIN II cases that regress within the population being screened and treated, and partly upon the proportion of women left untreated who return for follow-up screening before invasive disease develops. This strategy, which requires an ability to monitor women found to have CIN I or II, can be difficult and expensive in some settings. It also assumes that the various CIN grades can be accurately differentiated cytologically. In addition, in many cases where preinvasive disease is monitored rather than treated, it may prompt a level of patient anxiety that reduces the acceptability of this approach.

## Treating All CIN

Where cervical cancer rates are high but CIN monitoring and follow-up are difficult or unlikely, treating all CIN cases may be an appropriate strategy—particularly since no practical and affordable method yet ex-

ists to predict with certainty which CIN lesions will progress to cancer and which will not. Proponents of this approach argue that outpatient treatment (LEEP in particular) is now simple, fast, effective, inexpensive, and safe, producing very few complications (5). The principal drawback is that this approach could lead to unnecessary treatment or overtreatment, resulting in some side-effects or complications that could have been avoided, placing a potentially heavy burden on the health care system and providers, and raising potential costs. Clearly, the benefits of treating all lesions need to be weighed against the risks and costs of unnecessary treatment for some women.

Additional factors may need to be considered in assessing the need for CIN treatment of women infected with the human immunodeficiency virus (HIV), since some evidence suggests that the coexistence of HIV may alter the natural history of CIN. Some studies indicate that HIV-positive women may have higher prevalences of HPV and CIN, higher CIN grades, and higher CIN recurrence rates than uninfected women after standard therapies (8–10).

OUTPATIENT TREATMENT TECHNIQUES

Determining which outpatient techniques are most appropriate for a particular setting is an important part of establishing a feasible, cost-effective cervical cancer control program. Outpatient therapy is appropriate for visible lesions on the ectocervix when invasive cancer and endocervical involvement have been ruled out. Over the past several decades, numerous ablative and excision methods have been used to treat preinvasive cervical disease. Ablative methods, which destroy abnormal cervical tissue, include cryotherapy, cold coagulation, laser vaporization, and electro-surgery. Cone biopsy being an inpatient method, the one outpatient excision method available is LEEP.

Excision methods have the advantage of providing tissue specimens for histopathologic diagnosis (if available), which sharply reduces the possibility of overlooking invasive cancer. Since all treatment techniques are associated with recurrence rates of up to 10%, posttreatment cytologic follow-up at approximately three-month intervals for one year and annually thereafter is recommended wherever possible. It should be noted, however, that some clinicians believe longer follow-up intervals to be acceptable.

Of all the outpatient CIN treatment methods available, cryotherapy and LEEP hold the most promise for application in developing countries—because of their effectiveness, lack of side-effects, simplicity, and low cost. Cure rates range from 80% to 95%, depending on the method used and the severity of the lesions. It is also true, however, that each of these methods has advantages and disadvantages (see Table 1) that demand consideration.

Cryotherapy

The effectiveness of cryotherapy appears to be affected by the severity and size of the lesion. Reported cure rates range from 70% to 90% in women with CIN III. Some studies have indicated that treatment fail-

Table 1. Outpatient treatment options for preinvasive cervical lesions.

Method qualities	Cryotherapy	LEEP
Effectiveness	80–90%	90–95%
Side-effects	Watery discharge, infection risk	Bleeding
Anesthesia required	No	Yes
Tissue sample obtained	No	Yes
Power required	No	Yes
Cost of basic equipment/supplies	Relatively low (US\$ 1 000–3 000)	Relatively high (US\$ 4 000–6 000)

ure was significantly associated with large, high-grade cervical lesions, particularly those containing high-risk types of HPV (11). However, most researchers suggest that cryotherapy is appropriate for CIN III, provided that patients adhere to a rigorous follow-up procedure. Regarding its feasibility, cryotherapy does not require electricity and may therefore be especially useful in rural settings where accessibility and the technique's ease of use may outweigh minor differences in effectiveness.

### **Loop Electrosurgical Excision Procedure (LEEP)**

LEEP, also known as large loop excision of the transformation zone (LLETZ), is a method of outpatient excision biopsy and treatment. LEEP's primary advantage over destructive techniques is that it removes rather than destroys suspect tissue, thus producing a histologic sample for pathologic review. This allows diagnostic sampling, patient selection, and treatment in two visits (the "see and treat" approach, as described below); and since the entire transformation zone is excised for histologic analysis, such analysis can rule out the presence of invasive disease.

Studies indicate that LEEP may improve the accuracy of histologic CIN diagnosis beyond that obtained with colposcopically directed biopsy (12–14). One study that compared the histologic results of colposcopically directed biopsies and LEEP sampling performed on the same patients found that, compared to the LEEP results, the biopsy results underestimated CIN in 16% of the cases and overestimated it in 41% (15). In addition, LEEP's efficacy and patient acceptance compare favorably to other methods. The average cure rates for all CIN usually range from 90% to 98% after 3 to 12 months, and cure rates for CIN III/CIS are generally as high within this same time frame. Lesion size rather than grade appears to influence the results (16).

Regarding disadvantages, the primary complication is bleeding. In addition, LEEP requires more expensive basic equipment and supplies as well as a higher degree of training than cryotherapy.

### **IMPROVING FOLLOW-UP**

In many low-resource settings, especially rural ones, women's access to health services may be limited by their distance from clinics, transportation costs, and family or work responsibilities. Reducing the number of clinic visits required for screening and treatment could make it easier for women to receive the care they need.

One method that has been studied is the "see and treat" approach, which eliminates the need for women to wait for the results of directed biopsy before returning for treatment. Instead, this relatively new two-visit strategy relies on initial Pap smear screening (visit one) followed by colposcopic examination of women with abnormal results and subsequent treatment if necessary (visit two). Most studies using the see and treat approach have relied on LEEP as the treatment of choice, since in most developed country settings the histologic sample can be analyzed after treatment to confirm the diagnosis and ensure that invasive cancer was not missed. This approach shows promise of being more acceptable than others to patients, reducing service delivery costs, and (perhaps most important) reducing the number of patients lost to follow-up (17). Studies evaluating the feasibility of the see and treat approach, primarily in Europe, have found a high level of patient acceptance (18). The approach is not appropriate, however, when colposcopic findings are equivocal or suggest invasive cancer.

Unfortunately, in many developing countries (particularly in nonurban settings) the see and treat approach as practiced to date (with colposcope and histologic evaluation) may not be feasible. Another possible approach for reducing the

number of clinic visits would modify the see and treat approach so that only one visit would be required. As presented, this strategy, which has not yet been evaluated, would use acetic acid and a portable, inexpensive, low-power magnification device to detect CIN and facilitate outpatient treatment. Women would undergo aided magnified visual inspection to detect clear abnormalities; and, if treatment were indicated, they would be treated immediately with a low-cost outpatient method such as cryotherapy.

This one-visit strategy would probably be less accurate than conventional approaches and could result in some women being treated unnecessarily. Furthermore, if cryotherapy were used it would not be possible to confirm that all abnormal tissue had been removed. Still, in some settings the benefits in terms of treated disease and prevention of future disease might outweigh the risk of treatment-associated morbidity, especially in high-prevalence areas where screening and treatment are currently not being provided at all. At present, research is needed to determine the effectiveness and acceptability of such an approach and to ensure the existence of adequate systems for posttreatment follow-up.

## CURRENT CIN TREATMENT PRACTICES AND PREFERENCES: SURVEY RESULTS

The survey and guided interviews that were undertaken as part of this evaluation sought to determine the availability of CIN treatment interventions and to get an overview of current CIN treatment practices and preferences in less-developed countries. In all, 110 responses were received from 33 countries, with an overall return rate of 46%. Thirty-seven percent of the respondents were African, 32% were Asian, 22% were from Latin America or the Caribbean, and the remainder were from the Middle East (Turkey) or the former Soviet

Union (Armenia and Russia). Most respondents were clinicians specializing in women's health and public health. No attempt was made to send the survey to a representative sample of practitioners by region or facility level (19).

The survey brought out the following key points:

(a) Worldwide, it appears that cone biopsy and hysterectomy are being used more widely than alternative methods to treat CIN. Cone biopsy was being used extensively in all of the regions surveyed, and hysterectomy was being widely used in every region except Latin America, where the respondents indicated that cone biopsy was more widely used than other methods (see Figure 1).

(b) In many settings, all grades of CIN are treated, rather than only high-grade or severe conditions.

(c) Among low-cost methods, LEEP and cryotherapy appear to be used more widely by respondents in Asia, the Caribbean, and Latin America than by those in other regions. Neither method appears decisively preferred over the other (see Figure 2)—except in Latin America and the Caribbean, where the respondents indicated far greater preference for LEEP than for cryotherapy.

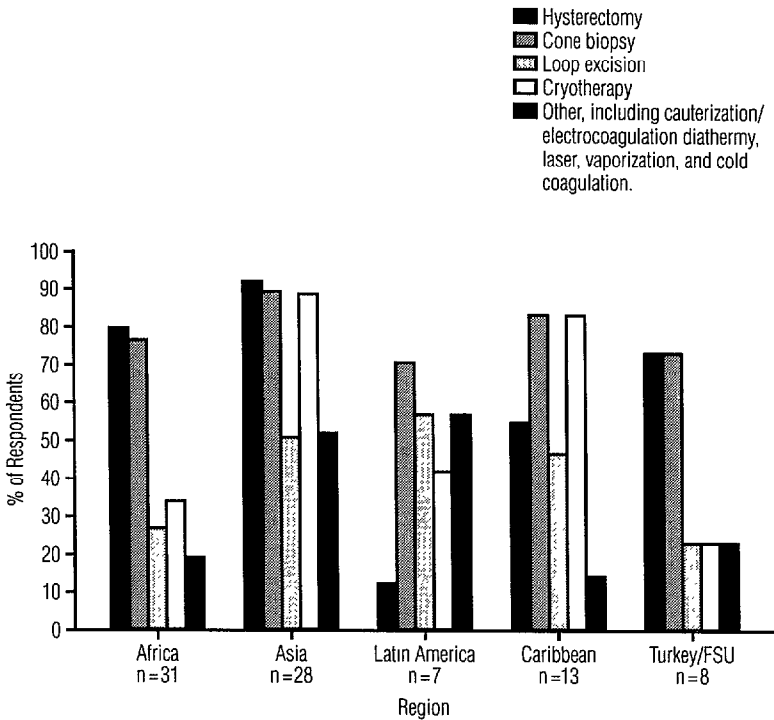
(d) Hysterectomy and cone biopsy were generally perceived by respondents to be more effective than other methods for treating severe dysplasia (CIN III/CIS). Of the low-cost methods, LEEP was perceived as a more effective method than cryotherapy for treating severe dysplasia.

(e) The vast majority of respondents indicated that gynecologists, rather than other clinical personnel, provide treatment.

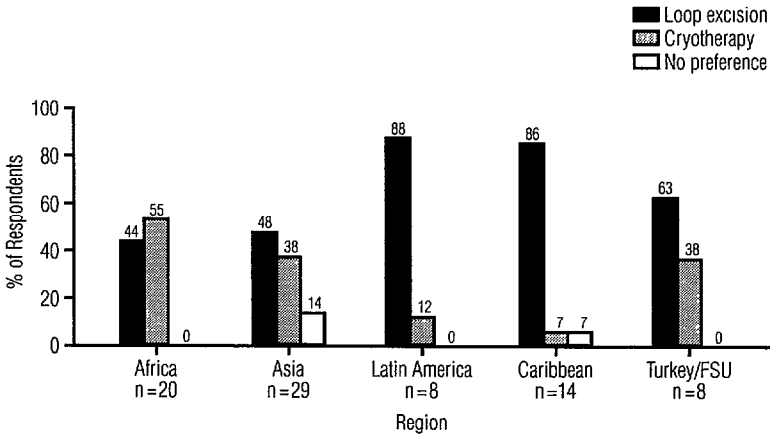
(f) Colposcopes and other basic equipment needed to provide treatment are not consistently or widely available in some settings.

Although this survey had evident limitations, the data obtained support the hy-

**Figure 1.** Percentages of survey respondents reporting the use of various kinds of CIN treatments, by region. It is likely that those who responded did so because they currently had some experience providing cervical cancer screening and/or treatment. Thus, it is assumed that the respondents were reporting on their own experiences as well as on the methods being used at their facilities.



**Figure 2.** Percentages of survey respondents who reported that they preferred LEEP, cryotherapy, or had no preference when these two CIN treatment methods were compared.



pothesis that greater efforts should be made in all developing regions to introduce simple, low-cost outpatient procedures such as cryotherapy and LEEP. The data also suggest that differing local conditions will require different introduction strategies. Further education of both clinicians and health program managers regarding the benefits of alternative low-cost approaches is clearly needed.

## CONCLUSIONS

To be effective, cervical cancer programs must reach more at-risk women with simple screening methods; diagnostic and treatment procedures that are cheap, easily applied, and effective; and appropriate follow-up protocols.

Of all the outpatient treatment methods available, cryotherapy and LEEP hold the most promise for application in developing countries because of their effectiveness, lack of side-effects, simplicity, and low cost. It should also be noted that the type of CIN treatment strategy chosen will influence both the success and cost-effectiveness of a cervical cancer control program. For example, the strategy of screening only higher-risk women (35 to 50 years old) and treating only high-grade lesions may reduce the burden on health care facilities while still achieving significant public health benefits.

The survey undertaken in connection with this presentation suggests that existing outpatient procedures such as cryotherapy and LEEP are not sufficiently available in many developing country settings, and that therefore clinicians must still rely primarily on cone biopsies and hysterectomies to treat CIN. Since these inpatient methods are much more costly than the outpatient techniques and require more infrastructure, many women do not have access to them. In addition, reliance on these methods makes inefficient use of scarce resources. The survey results also

suggest that existing practices involving treatment of all CIN cases should be re-evaluated to ensure that the most rational, appropriate, and cost-effective CIN treatment protocols are being used.

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